IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

H. William Bosch et al.

Title:

NOVEL NIMESULIDE COMPOSITIONS

Appl. No.:

10/697,703

Filing Date:

10/31/2003

Examiner:

Tristan J. MAHYERA

Art Unit:

1615

Confirmation 8369

Number:

DECLARATION UNDER 37 CFR 1.131

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Sir:

I, H. William Bosch, hereby declare and state that:

- I am a citizen of the United States, residing at 237 Rodney Circle, Bryn Mawr, PA 1. 19010.
- 2. At the time of events detailed in paragraph 4, infra, I was an employee of Elan Drug Delivery, Inc., with offices at 3500 Horizon Drive, King of Prussia, PA 19406.
- I am a co-inventor of the invention disclosed and claimed in the above-referenced 3. application.

- 4. Prior to June 27, 2003, I instructed my associates, as part of my supervisory role, to prepare nimesulide compositions comprising particles of nimesulide or a salt thereof having an effective average particle size of less than 2000 nm and at least one surface stabilizer adsorbed on the surface of the particles. My work relating to preparing the nimesulide compositions, which occurred prior to June 27, 2003, is documented in the attached exhibits.
- 5. As shown in Exhibit A (Notebook No. 5822, pages 006-008), the formulation comprising 5% nimesulide and 1% Plasdone® S-630 provides a stable nanoparticulate nimesulide composition.
- 6. As shown in Exhibit B (Notebook No. 5822, pages 009-011), the formulation comprising 5% nimesulide and 1% Plasdone® S-630 provides a stable nanoparticulate nimesulide composition.
- 7. As shown in Exhibit C (Notebook No. 5822, pages 012-014), the formulation comprising 5% nimesulide, 1% Plasdone® S-630 and 0.2% DOSS provides a stable nanoparticulate nimesulide composition.
- 8. As shown in Exhibit D (Notebook No. 5822, pages 015-017), the formulation comprising 5% nimesulide, 1% Plasdone® S-630 and 0.05% sodium lauryl sulfate (SLS) provides a stable nanoparticulate nimesulide composition.

H. William Bosch

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

June 27, 2008

Date

H. William Bosch



LABORATORY NOTEBOOK NO. 5822 Page

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	() / (API ; 1.16	5-630)	
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n. in i		_		and a management of the state o
Batch Record	ior Dispersio	n Technology N	<u> Iilling Procedu</u>	res
I. General In	formation			
[None				
Name Date	Christian	Werty Bulide 1°i		
Formula	5 % - Nima	Redicte ioi	C-/24	
Continued on Page	007	2 AU (M) 1 - (4	J - 1/20	
	-			
II. Quantities I	Dispensed			
	Quantity	Туре		
Media	80 6		Source	Lot Number
Drug Substance	4-25	Polymill 200 Nimery lide	DOW / PMRS	
Stabilizer	0.85	5-630	Sigma	
Water	79.9	PI		
Other				
Milling Method Mill Speed Temperature	Dyna mill	(150 u katch c	hamber) F91	5 @ Rm.205
Temperature	1 10 10 12			
IV. Notes				
Mail: On:				
Milling Time: 9:5		milling ; 10	31 - first J	Sample
	o assina	Jumple : 11:	41 - third	Sample.
	0 - Harres	<u>t-</u>		
Quantity retained post-	milling: forgot	to file not	Mader 1.	
		THE VIT	media before	Weighing
, 0, ,		4	W. W.	
not tilter ou	t media in	itally and	discarded ~	1/2 suspension
ter filtration	left ~20	mh of mon	in from such	1/z suspension
		2	HEE SUIP	ension Aco
			(C	cont. on pg. 007
DENTIAL	ο, ,	AOI	. //	
DENTIAL	Signature	Chity 7. W Miles Dez	leit	Date



Title Nimeralide	(5 1/2	API	<u>, </u>	1 6/2	5-630)
	+	_	,			

(cont. from pg. _______)

Batch Record for Dispersion Technology Milling Procedures

Name	Christian Wertz
Date	1
Formula	5% Nimetulide 1% 5-630
Continued from page	006

IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 8514870103D)
Standards Measured	Lot # 22579; mean = 200; Dyke Sci; 200 nm Std

Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments
46	173	156	285	No Sonication
	169	148	280	60 See. Sinication
60	150	124	256	No senication
	144	121	243	60 sec. sonication
108	3461	140	14961	No Sonication
102	131	111	218	60 Sec. Sonication
197	10794	318	33156	No Sonication
2 4.	140	112	246	60 Sec. sonication
3 day	195	142	337	No Senication
	143	115	249	60 Sec. Sinication

it Cansed by r	to aggregate offen between (0-108 minutes duction in particle Size (Increase in Surface area)	
* Can increase	1d not be compensated for with 11% 5-630 - 5-630 Concentration or add additional Stabilizer data in folder #2	
CONFIDENTIAL Review	Signature Ch. L. J. Wuty Date ed and understood by Miles Dell Date	

	Information					
Name Date	Chr.	ittan F. We	evtz-			
Formulation	15	10/0 Nimesial	ide 1º	1u S-63	0	
Notebook referenc	e					
Continued on page						
II. Particle S	Size Data					
Particle Size Analy		HORIBA L	A-910 (5#	+ 851487	01030)	
Standards Measure	d	Lot # 22	569; mean	= 200 nm	Duke Sci; 200	inm Std.
Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Co	omments
3 days	5 'L	195	142	339	No Senuit	
5 days	5.0	143	115	249	60 sec. So	
5 days	5°C	176	1/2	322	no Sonicat	ion
7 dans	5°C	138	113	235 342	60 S Sony	
	5°C	139	110	248	no Sonication 60 S Sonic	
14 days	5.0				30,00	
	5.0					
					<u> </u>	
1						
		1	I			
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CIUII					
Title Nimerulide	(5 % ATI	, 2 % S	-630)		
(cont. from pg) - mix J-630 Str - add polymill 3	vly into D. 200 w/ qe	I Hzo W ntle manual	mild str Striving	ring until disported	
- add API w/	gentle stri	iring until	thoroughly	mixed	
Batch Record f		Technology M	illing Procedi	ures	
Name Date Formula Continued on Page	Christian Y 5 % Nim	Verts Vévilide, 2	% S-630		
II. Quantities D					
	Quantity	Туре	Source	Lot Number	
Media	30.6	Polymill 200	DOW	MM 00/D12	
Drug Substance	4.25	Nimesulide	Sigma	117/1/10/19	
Stabilizer Water	1.70 79.05	S-630 PI	ISP Tech.	ML900012974	
Other	1/22	-			
Milling Method Mill Speed Temperature IV. Notes		od ce baten chu	amber) F9.	15@ Rm 205	
Milling Time: 8:15		tch; 9:15 el.; 11:15	Harvest	<i>(</i>	
Quantity retained post-	milling: 49.6	g (58 %)			
			_	(cont. on pg. 0/0)
CONFIDENTIAL	Signature	Chita T.	With	Date	
Reviewed a	nd understood by _	N. William	in Bosch	Date	

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010 of 200

Title <u>Nimerolide</u>	(5% API	, 2 %	S-630)	
(cont. from pg)				

Batch Record for Dispersion Technology Milling Procedures

Name	Christian Westy
Date	9
Formula	5 % APF 2 %)-630
Continued from page	009

IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 8514870103D)
Standards Measured	Lot # 22529 mean = 200 nm; Pukesci 200 nm Std.

Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments
60	156	136	255	No sonication
	156	134	258	60 S sonication
120	125	109	201	no sonication
	122	107	193	60 5 Sonication
180	144	111	260	no sonication
	132	111	221	60 S Sonication

· Pata in folder #2 supplementary folder OFW-5822 A

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JOHI IDENTIAL	Signature	Cluth 7	· Wit	·	Date	**********
Reviewed and	understood by	W. Wills	am Bos	sch	Date	······································



Chris	Hun Newtz				
	, ,,,				
					
5 %	API 26	5-630			
Data					
Used	HORIBA L	A-910 (S# 85148	70103D)	
	Lot # 2256	9 : mean = 2	popm; Tuke	Sci j Coopm Stail	
Storage Conditions	Mean, nm	D50, nm	D90, nm		
	141	111	253	no sonication	1
5.6	130	110			1
500	138	///	242		
5.6		110			-1
	<u> </u>				
					_
			241	60 S Sonication	
		125	Z66	no sonicution	-
	145	121	246	60 & Sonication	
	I				
	-		1		
	Storage Conditions 5 °C 5 °C 5 °C	Storage Mean, nm	Storage	Storage	Storage Mean, nm D50, nm D90, nm Comments



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Name	nformation Christian F. W	ertz		
Date Formula	5% API, 1% S	-630, 0.2% DOSS		
Continued on Page	013			
II. Quantities	Dispensed			
Madi-	Quantity	Туре	Source	Lot Number
Media Drug Substance	80.6	polymill 200	pow	MM001012
Stabilizer	4.15	Nimesulida	Sigma	11741019
Water	0.85	1-630	ISP Tech.	ML900012974
Other	79.73	PI	Cytec	SD 0041815
Milling Method Mill Speed	Dynomill (150 cc 4200 rpm	batch chamber) F915 @	room 205	
Temperature	10 C			
Milling Time: \$:2		ch ; 9°20 1	§ Sample	

LABORATORY NOTEBOOK NO. 5822 Page 013 of 200

)ate		an F. Wertz			
		PI, 1% S-630, 0	29/ DOSS		
ormula Continued from pa			.2 /6 DO33		
V. Particle S	Size Data				
article Size Analy	vzer Used	HORIBA LA	N-910 (s#: 851	14870103D)	
Standards Measure		Lot #: 22569); mean = 204	; Duke Sci.; 200 nm standard	
Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments	
60	172	154	278	no sonication	
14	172	156	2.80	60 S Smication	
120	131	111	216	60 S SINICATION	
	130	//0	217	60 3 SIMICATION	······································
	_				
			<u> </u>		-
	_				
			<u> </u>		
			-		
			<u> </u>		



Title Nimesulide	5 % API, 1%	5-630, 0.2%	P055
(cont. from pg013)			

Particle Size Stability for Dispersion Technology Formulations

General Information

Name	Christian F. Wertz
Date	
Formulation	5% API, 1% S-630, 0.2% DOSS
Notebook reference	
Continued on page	

II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = 203 ; Duke Sci.; 200 nm standard

Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
1 day	5°C	136	116	223	no Senication
· · · · · · · · · · · · · · · · · · ·	500	137	116	224	60 5 Sonication
2 duy	5°C	143	121	238	No Sonication
'	500	144	122	241.	60 s sonication
6 da ₁	5°C	149	133	239	no Sonication
l	5.0	<u> 151</u>	135	242	60 & Sonication
7 day	5°C	i 60	143	259	no sonication
,	5°C	163	146	261	60 S Sonication
21 day	5°C	162	150	252	no senication
	5°C	166	155	255	60 & Sonication
35 day	5°C	180	172	276	no sonication
J	5°C	187	180	280	60 5 somiation

· Data in tolder + 2 Supplementary tokler CFW-5822 A

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CONFIDENTIAL	Signature	Chitu	7. With	Da	ite	
Reviewed and	understood by	A-Will	ram bosu	Da	- ite	



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le <u>Ninesulide</u>	5 1/0 API,	1% 5-630 ,	0.05% 52	5
ont. from pg.	`			
nt. nom pg.	. /			
- Dissolved	5-630 in Hzo.	followed by	SLS under 9	ertle mixing
- SLS dissolv	5-630 in Hzo. ed very rap	dly w/ very	11the form	
- Mastina Ministerior and Control of the Control of	,			
Batch Record	for Dispersion	Technology M	illing Procedur	es
Dated Record	101 2/102010101			
I. General In	formation			
[Di	Christian F. Wertz			
Name Date	Christian F. Well			
Formula	5% API, 1% S-63	0, 0.05% SLS		
Continued on Page				
4. Quantities	Dispensed			
	Quantity	Туре	Source	Lot Number
Media	80.6	Polymill 200	DOW	MM001012
Drug Substance	4.25	Nimesulide	Sigma	117H1019
Stabilizer	0.85	S-630	ISP Technology	ML900012974
Water	79.86	H2O	DI	
Other	0.04	SLS		
III. Process Pa	rameters			
Milling Method	Dynomill (150 cc ba	itch chamber) F915 (@ room 205	
Mill Speed	4200 rpm			
Temperature	10 C			
IV. Notes				
Milling Time: 9:	in the fatel	; 9:22 1 <u>st</u>	Samble	
	22 Start batch	· 9:22 /5	Sample	
Quantity retained po	st-milling: 69.4 9	(80.7 ht	%)	
· Mill began Leukin	ig after first so	umple was tak	en from mill	
		,		(cont. on pg. 016
ONFIDENTIAL	0:	111 + 7	11 +	Date_
	Signature ed and understood by	Chih To	With,	Date
Review	ed and understood by	M-Willen	in Bosch	Date
Review	ed and understood by	H-Wullin	in Dosch	Date

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S% API, 1% S-630, 0.05% SLS	HORIBA LA-910 (s#: 8514870103D) Interest	Particle Size Data	Particle Size Data HORIBA LA-910 (s#: 8514870103D) Iticle Size Analyzer Used HORIBA LA-910 (s#: 8514870103D) Indards Measured Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Indards Time Mean, nm D50, nm D90, nm Comments Indards Time Indards Mean, nm D50, nm D90, nm Comments Indards Time Indards Mean, nm D50, nm D90, nm Comments Indards Mean, nm D90, nm D90, nm D9	Particle Size Data HORIBA LA-910 (s#: 8514870103D) Size Analyzer Used HORIBA LA-910 (s#: 8514870103D) Indiards Measured Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Indiards Time Mean, nm D50, nm D90, nm Comments Comments Comments	Particle Size Data HORIBA LA-910 (s#: 8514870103D)	Particle Size Data HORIBA LA-910 (s#: 8514870103D) Indards Measured HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Iapsed Time Mean, nm D50, nm D90, nm Comments 60	Particle Size Data	Particle Size Data HORIBA LA-910 (s#: 8514870103D) Iticle Size Analyzer Used HORIBA LA-910 (s#: 8514870103D) Indards Measured Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Indards Time Mean, nm D50, nm D90, nm Comments Indards Time Itin I	Particle Size Data HORIBA LA-910 (s#: 8514870103D) Iticle Size Analyzer Used HORIBA LA-910 (s#: 8514870103D) Indards Measured Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Indards Time Mean, nm D50, nm D90, nm Comments Indards Time Itin I	Particle Size Data	Particle Size Data
Particle Size Analyzer Used HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Elapsed Time Mean, nm D50, nm D90, nm Comments	HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Mean, nm	HORIBA LA-910 (s#: 8514870103D) Indards Measured	ticle Size Analyzer Used Indards Measured HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Lapsed Time Mean, nm D50, nm D90, nm Comments	icle Size Analyzer Used Idards Measured HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard apsed Time Mean, nm D50, nm D90, nm Comments 60 174 154 288 no sinication 176 157 271 60 S Senication 104 175 no suncation	ticle Size Analyzer Used Indards Measured HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60 174 154 288 no Sinication 176 157 271 60 S Sonication 104 175 no Sinication	HORIBA LA-910 (s#: 8514870103D) Indards Measured	ticle Size Analyzer Used Indards Measured HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60 174 154 288 no Sinication 176 157 271 60 S Senication 104 175 no Sinication	ticle Size Analyzer Used Indards Measured HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Clapsed Time Mean, nm D50, nm D90, nm Comments 60	HORIBA LA-910 (s#: 8514870103D) Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Elapsed Time Mean, nm D50, nm D90, nm Comments 60
Standards Measured Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Elapsed Time Mean, nm D50, nm D90, nm Comments 60 174 154 288 no Senication 176 157 271 60 S Senication 120 116 104 175 no Senication	Mean, nm D50, nm D90, nm Comments 174 154 288 no sinication 176 157 271 60 S Sonication 176 175 no senication	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Clapsed Time Mean, nm D50, nm D90, nm Comments	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard apsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Clapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Comments Comments	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Comments Comments
Standards Measured Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Elapsed Time Mean, nm D50, nm D90, nm Comments 60 174 154 288 no Sinication 176 157 211 60 S Sonication 120 116 104 175 no Sinication	Mean, nm D50, nm D90, nm Comments 174 154 288 no Sinication 176 157 271 60 S Sonication 176 175 no Sinication 176 177 17	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Clapsed Time Mean, nm D50, nm D90, nm Comments	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard apsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Clapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard lapsed Time Mean, nm D50, nm D90, nm Comments 60	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Comments Comments	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard Comments Comments
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. General In Name Date Formulation	Christian	a E Wod-			
Date	Christia	C Waster			
		IF. WEITZ			
UOITHUIATION	50/ ADY	1% S-630, 0.05	0/ CI C		
Notebook reference		1 70 3-030, 0.03	√0 OLO		
Continued on page					
I. Particle Si	ze Data				
article Size Analyz	zer Used	HORIBA LA	-910 (s#: 85148	370103D)	
tandards Measured		Lot #: 22569;			200 nm standard
Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
3 day	5-16	j 23	108	192	no Sonication
	5°C	123	108	/93	60 S Somication
5 day	5°C	127	110	203	no Sonication
7 duy	5°L	12 7 133	110	205 219	no sonuation
1 44 4	5°C	134	113	219	60 S Somication
21 day	5°L	126	110	199	m sonication
	5°C	127	109	205	60 S Someation
35 day	5°C	141	/26	234 237	no Sonication
	500	142	119	237	60 S Somication